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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,580	04/02/2001	Michael J. Eppihimer	GFN-5398	9952

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	14

DATE MAILED: 12/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/825580	Applicant(s) EPPICHMER
	Examiner GAMBEL	Art Unit 1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10/16/01

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 10/16/01 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 1

DETAILED ACTION

1. Applicant's election with traverse of Group I in Paper No. 13 is acknowledged. Regarding applicant's comments about undue burden and common classification, the MPEP 803 states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

In the previous Restriction Requirement, mailed 9/23/02 (Paper No. 11), applicant was invited to clarify whether Groups I, II and III are indeed different Groups and or to distinguish the Groups, given the differences in the preamble of the independent claims.

Although applicant did not distinguish the Groups other than to indicate that there was no serious burden in examining all the claims at once, it appears that the claims set forth in Groups II and III recite inherent properties (i.e. "Increasing the movement of cells relative to blood cells" and "inhibiting the effect of thrombus-inducing agents") of "methods of treating or inhibiting thrombosis in a subject comprising administering a composition comprising an effective amount of a P-selectin antagonist" set forth in Group I.

Therefore, in the interest of compact prosecution, claims 1-27 employing PSGL-1 as the P-selectin antagonist are under consideration in the instant application.

If applicant disagrees with this assessment, then such claims drawn to previously indicated Groups II and III will be subject to removal from consideration as they on the elected invention of Group I.

2. Formal drawings, filed 10/16/02, comply with 37 CFR 1.84.

3. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PSGL-1, including the P-selectin binding domains and fragments, does not reasonably provide enablement for any "P-selectin antagonist" or "P-selectin binding (or inhibiting) fragment" of PSGL.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "antagonists" or "fragments with "P-selectin activity" that would enable that any "antagonist" or "fragment" of PSGL-1 would be effective or predictive of inhibit thrombosis.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. inhibit thrombosis) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of "PSGL-1 fragments and antagonists" and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant application, it is noted that various mutations, substitutions and the like provide a range of activities, no all which are necessarily predictive of "PSGL-1 fragments and antagonists to inhibit thrombosis". It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences as essential for in vivo characterization of their therapeutic potential to treat atherosclerosis. A person of skill in the art could not predict which particular amino acid sequences of "PSGL-1" are essential to "fragments and antagonists" and could be used in a therapeutic methods.

The success of state of the art structure-based strategies for inhibitor design is highly unpredictable. For example, Kuntz (Science 257:1078-1082, 1992) on page 1080, column 3, discloses that as little as 2% of compounds predicted to inhibit specific enzymatic or receptor systems actually show inhibition in the micromolar range. Kuntz further discloses that "optimization" of these compounds has proven even more problematic. Therefore, in view of the unpredictability in the art, and in view of the insufficient guidance and working examples in the specification, the quantity of experimentation required by one skilled in the art to practice the invention undue.

Because of the lack of sufficient guidance and predictability in determining which modifications would lead to "PSGL-1 fragments and antagonists to inhibit thrombosis" and that the relationship between the sequence of a protein / peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of other functional PSGL-1 fragments and analogs to treat atherosclerosis".

Without sufficient guidance, the changes which can be made in the structure of "PSGL-1 fragments and antagonists to inhibit thrombosis" is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant is invited to the limit the claimed antagonists to "PSGL-1" and the "P-selectin ligand activity" of "PSGL-1 fragments to "PSGL-1" and "PSGL-1 fragments" with those activities (e.g. "binding or inhibiting") disclosed in the specification as filed and to those activities which can be readily measured.

Applicant is reminded to provide sufficient written support for any amended "limitations" to avoid new matter issues. See MPEP 714.02 and 2163.06

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8 Claims 1-4, 8-13, 16-18 and 20-27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Cummings et al. (U.S. patent No. 5,464,778) (see entire document).

Cummings et al. teach the use of PSGL in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis (see column 18, paragraphs 5-8; columns 19-20). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 3) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various acute and chronic conditions associated with thrombosis with PSGL and fragments thereof and the properties of said PSGL and fragments thereof at the time the invention was made.

Cummings et al. also teach dosage ranges (e.g. 0.2 to 30 mg/kg body weight) for the treatment of inflammatory disorders (column 21, paragraph 1). Although this paragraph discloses carbohydrate inhibitors, the ordinary artisan would have immediately envisaged that this broad dosage range would have included other inhibitors (e.g. column 18, paragraph 4) as dictated by the specific condition (column 21, paragraphs 2-3). Also, given the nature of the acute and particularly the nature of chronic thrombotic conditions, one of ordinary skill at the time the invention was made would have provide the PSGL prior to thrombus formation.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). See MPEP 2112-2112.02.

9. Claims 1-5, 7-18 and 21-27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Larsen et al. (U.S. Patent No. 5,840,679) (see entire document).

Larsen et al. teach the use of PSGL (e.g. ; columns 7-8, columns 13-18 and Examples), including fragments (e.g. columns 9-10) and fragments fused to carrier molecules such as immunoglobulins (e.g. chimeric forms of said PSGL (column 9-10, overlapping paragraph) to treat conditions characterized by P-selectin mediated intercellular adhesion, such as myocardial infarction (columns 15-16, overlapping paragraph), including its combination with other pharmaceutical compositions, including anti-inflammatory and thrombolytic or anti-thrombotic agents (e.g. columns 16-18) (see entire document, including Summary of the Invention; Detailed Description of the Invention). Larsen et al. also teach various modes of administration and dosing (e.g. liposomes, pharmaceutical carriers), including combinations of agents would be provided in therapeutically effective amounts either serially or simultaneously sufficient for the needs of the patient, including the nature and severity of the condition being treated according to the attending physician as well as doses ranges from about 0.1 ug to about 100 mg of isolated PSGL per kg body weight (columns 16-18). Larsen et al. teach soluble forms and fragments thereof which binds P-selectin comprising the same or nearly the same regions encompassed by the claimed human PSGL sequences (e.g. columns 9-15). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various conditions associated with thrombosis with PSGL and fragments thereof and the properties of said PSGL and fragments thereof at the time the invention was made

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999); Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). See MPEP 2112-2112.02.

10. Claims 1-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) and in further evidence of Maugeri et al. (Thrombosis and Haemostasis 72: 450-456, 1994).

Cummings et al. teach the use of PSGL in the treatment of leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis (see column 18, paragraphs 5-8; columns 19-20, overlapping paragraph). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 3) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3). The claimed functional limitations would be expected properties of the referenced methods of treating atherosclerosis with PSGL and fragments thereof.

Cummings et al. differs from the claimed PSGL by not disclosing particular human PSGL sequences and domain structure thereof. Larsen et al. teach the structure, including the domain structure and the use of PSGL-derived fragments which are the same or nearly the same as that claimed (see columns 9-15).

Larsen et al. teach the use of PSGL (e.g. ; columns 7-8, columns 13-18 and Examples), including fragments (e.g. columns 9-10) and fragments fused to carrier molecules such as immunoglobulins (e.g. chimeric forms of said PSGL (column 9-10, overlapping paragraph) to treat conditions characterized by P- or E-selectin mediated intercellular adhesion, such as myocardial infarction (columns 15-16, overlapping paragraph), including its combination with other pharmaceutical compositions, including anti-inflammatory and thrombolytic or anti-thrombotic agents (e.g. columns 16-18) (see entire document, including Summary of the Invention; Detailed Description of the Invention).

Although Cummings et al. and Larsen et al. do not disclose all of the effective amounts recited in the instant claims 18-20, Cummings et al. and Larsen et al. teach the art known provision effective amounts of PSGL which inhibit P-selectin binding to treat thrombotic conditions to meet the severity of the condition and the needs of the patients. Therefore, the modes of administration and dosages encompassed by the claimed invention (claims 17-20) would have been met by the ordinary artisan at the time the invention was made to meet the severity of the conditions and the needs of the patients. For example, Larsen et al. also teach various modes of administration and dosing (e.g. pharmaceutical carriers), including combinations of agents would be provided in therapeutically effective amounts either serially or simultaneously sufficient for the needs of the patient, including the nature and severity of the condition being treated according to the attending physician (columns 16-18).

Although Cummings et al. and Larsen et al. do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer PSGL-1, fragments and chimeric constructs thereof, provided they had the properties of inhibiting PSGL-1-mediated interactions and inflammatory responses, as taught by Cummings et al. and Larsen et al. to treat patients with various thrombotic conditions. Given the teachings of Cummings et al. . and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit thrombosis, to increase the movement of cells relative to blood vessels and to inhibit the effect of thrombus-inducing agents, as properties of such treatment of PSGL-1-mediated interactions and inflammatory responses. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 25-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) as applied to claims 1-27 above and in further evidence of Maugeri et al. (Thrombosis and Haemostasis 72: 450-456, 1994) and Johnston et al. (J. Immunol. 159: 4514-4523, 1997).

The teachings of Cummings et al. and Larsen et al. are set forth above.

Cummings et al. and Larsen et al. differ from the claimed methods by the claimed methods by not disclosing the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions as taught by Maugeri et al. and

Maugeri et al. teach that is was known at the time the invention was made that LTC_4 was one of the biologically active substances that play a role in inflammation and thrombosis (see entire document). Further, Maugeri et al. teach that anti-P-selectin antibodies can inhibit LTC_4 production (see Abstract, Results and Discussion). Further, Marugeri et al. discuss that neutrophil-platelet interaction via P-selectin plays a role in LTC_4 cooperative synthesis, which play a significant role in sever pathophysiological situations including inflammatory and cardiovascular diseases (see Abstract, Results and Discussion).

Johnston et al. teach that anti-P-selectin antibodies can inhibit inflammatory conditions, including LTC_4 induced leukocyte rolling in vivo (see entire document, including Abstract, Results and Discussion).

Again, although Cummings et al. and Larsen et al. do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions, as evidenced by Maugeri et al. and Johnston et al.. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made. Further, both Maugeri et al. And Johnston et al. teach that inhibiting P-selectin-mediated events results in the inhibition of thrombus-inducing biological substances, including LTC_4.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer PSGL-1, fragments and chimeric constructs thereof, provided they had the properties of inhibiting PSGL-1-mediated interactions and inflammatory responses, as taught by Cummings et al. and Larsen et al. to treat patients with various thrombotic conditions. Given the teachings of Cummings et al. . and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit the effect of thrombus-inducing agents, as properties of such treatment of PSGL-1-mediated interactions and inflammatory responses. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

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